(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 809 512 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
03.04.2002 Bulletin 2002/14

(21) Application number: **96903969.2**

(22) Date of filing: **08.02.1996**

(51) Int Cl.[7]: **A61K 38/23**, A61K 9/06, A61P 19/08, A61P 19/10

(86) International application number:
PCT/EP96/00446

(87) International publication number:
WO 96/24370 (15.08.1996 Gazette 1996/37)

(54) PHARMACEUTICAL NON INORGANIC SALINE SOLUTIONS FOR ENDONASAL ADMINISTRATION OF A CALCITONIN

PHARMAZEUTISCHE NICHTINORGANISCHE SALZLÖSUNGEN FÜR ENDONASALE VERABREICHUNG EINEs CALCITONINs

SOLUTIONS PHARMACEUTIQUES SALINES NON inORGANIQUES A ADMINISTRATION ENDONASALE D'UNE CALCITONINE

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI NL PT SE
Designated Extension States:
SI

(30) Priority: **08.02.1995 EP 95101681**

(43) Date of publication of application:
03.12.1997 Bulletin 1997/49

(73) Proprietor: **THERAPICON SRL**
I-20146 Milan (IT)

(72) Inventors:
- **VERONESI, Paolo, Alberto**
  I-20146 Milan (IT)
- **VERONESI, Anna Maria**
  I-06083 Bastia (IT)
- **PESCHECHERA, Emanuela**
  I-20125 Milano (IT)

(74) Representative:
Baverstock, Michael George Douglas et al
BOULT WADE TENNANT,
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT (GB)

(56) References cited:
EP-A- 0 122 036
EP-A- 0 358 234
EP-A- 0 490 549
EP-A- 0 504 483
WO-A-93/06854

- **CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 Columbus, Ohio, US; abstract no. 97319, NOGATA YOSHIHIKO ET AL: "AQUEOUS COMPOSITIONS CONTAINING CALCITONINS" XP002005905 & DATABASE WPI Section Ch, Week 9211 Derwent Publications Ltd., London, GB; Class B04, AN 92-85873 & JP,A,04 029 938 (TOYO JOZO KK) , 31 January 1992 & PATENT ABSTRACTS OF JAPAN vol. 16, no. 194 (C-938), 11 May 1992 & JP,A,04 029938 (TOYO JOZO CO LTD), 31 January 1992,**

EP 0 809 512 B1

Description

[0001] The invention is concerned with novel pharmaceutical non saline solutions for endonasal administration containing a natural or modified calcitonin, more preferably salmon calcitonin or carbacalcitonin (elcatonin), having enhanced organoleptic characters and a better patient's compliance.

[0002] Calcitonins are well-known long chain polypeptides used for convenient prophylaxis and therapy of some diseases, like Paget's disease, hypercalcemia and osteoporosis.

[0003] Calcitonin salmon is widely and efficiently adopted for the treatment of the above indications, so that specific monographs have been included in the most qualified pharmacopoeias like Eur. Ph. II Ed., DAB 10 (1991), BP 88, F. U. IX Ed..

[0004] The above pharmacopoeias indicate that calcitonin salmon (dry active ingredient), as acetate salt, shall contain minimum 4,000 I.U. per milligram (biological assay) and not more than 10 % by weight of water and not more than 15 % by weight of acetic acid. Storage condition at about 4°C/8°C is also prescribed for the powder stability.

[0005] Already there have been described saline compositions of calcitonin salmon for endonasal administration, which are stabilized with an appreciable quantity of acetic acid, but the presence of acetic acid results in the entire composition having a very unpleasant odour of acetic acid.

[0006] Additionally in these compositions it is not possible to analytically establish the exact aliquot of acetic acid included in the active ingredient calcitonin (maximum 15 % by weight) and the part of acetic acid, which has been added to the formulations as stabilizing excipient.

[0007] In other previous compositions (DE-A 33 35 086), hydrochloric acid has been used to adjust the pH value of the solution. This practice is also very inconvenient because of hydrochloric acid is able to remove acetic acid from the calcitonin acetate salt, thus producing an undesired liberation and odour of acetic acid.

[0008] Other publications teach that aliquots of calcitonins, for endonasal administration, therapeutically bioequivalent to those administered by parenteral route, are normally absorbed through the nasal mucosa and are also generally well tolerated. Calcitonins, specifically calcitonin salmon, as acetate salt, is remarkably unstable and, when it is not suitably formulated (bacterial contamination, unsuitable pH values, packed in non nitrogen atmosphere) or stored at temperatures above 8°C, it may develop some degradation products, which have already been described by some authors in the published literature.

[0009] In fact in some compositions (DE-A 33 35 086), benzalkonium chloride is used to avoid the bacterial contamination during the storage period and/or utilization, but several studies have indicated that this preserving agent produces some undesirable secondary effects (Am. J. Ophatalmol. 105 (6) [1988] pages 670 to 673; Contact Dermatitis 17 (1) [1987] pages 41 to 42; Cutis 39 (5) [1987] pages 381 to 383).

[0010] Thus the problem underlying the present invention is to create novel pharmaceutical solutions for endonasal administration containing a natural or modified calcitonin, preferably salmon or alternatively carbacalcitonin (elcatonin), or its pharmaceutically acceptable salts, which are odourless and tasteless and thus have improved patient's compliance and which do not have the undesirable secondary effects of known compositions but which permit a complete and accurate analysis of the active principle and develop less degradation products during storage.

[0011] Surprisingly this has been attained by the present invention.

[0012] The invention is based on the surprising recognition that non inorganic saline aqueous solutions containing natural or modified calcitonin as acetate salt (active principle) and besides water only organic excipients, described in the most common pharmacopoeias, like pharmaceutically acceptable acids, bases, suspending agents and, optionally C_{1-4} alkylesters of p-hydroxybenzoic acid fulfil the above requirements. Surprisingly it has been found that such a composition as defined below is very suitable for endonasal administration, when applied to the nasal mucosa and it is odourless and tasteless, properties that improve the patient's compliance. Moreover the inventive composition allows performance of a complete and accurate analysis of the active ingredient calcitonin salmon (including its volatile impurities, like acetic acid) and minimizes the development of degradation products during the ageing period.

[0013] The present invention provides pharmaceutical non inorganic saline solutions for endonasal administration containing:

a) a natural or modified calcitonin, preferably salmon or alternatively carbacalcitonin (elcatonin), as its pharmaceutically acceptable salts,
characterized in that they further contain the organic excipients described in the most common pharmacopoeias
b) N-(methyl)-glucamine [meglumine]
c) tromethamine,
d) citric acid
e) polyvinylpyrrolidone ranging from K15 to K120.

[0014] The active principle and the said organic excipients are dissolved in water.

[0015] Advantageously the calcitonin is salmon calcitonin, human calcitonin, eel calcitonin, carbacalcitonin (elcatonin), chicken calcitonin or porcine calcitonin.

[0016] Preferred solutions according to the invention contain

a) the calcitonin or its pharmaceutically acceptable salts in concentration of 250 I.U./ml to 5,000 I.U./ml,

b) the N-(methyl)-glucamine in concentrations of 2.0 to 5.0 mg/ml,

c) the tromethamine in concentrations of 1.0 to 4.0 mg/ml,

d) the citric acid in concentrations of 5.0 to 9.0 mg/ml and

e) the polyvinylpyrrolidone ranging from K15 to K120 in concentrations of 5 to 25 mg/ml.

[0017] It is particularly preferred that the concentration of the calcitonin or its pharmaceutically acceptable salts [a)] is from 400 I.U. to 1,200 I.U./ml.

[0018] Furthermore it is particularly preferred that the concentration of the N-(methyl)-glucamine [b)] is from 2.5 to 4.0 mg/ml.

[0019] Moreover it is particularly preferred that the concentration of the tromethamine [c)] is 1.5 to 4.0 mg/ml.

[0020] It is also particularly preferred that the concentration of the citric acid [d)] is from 6.0 to 8.0 mg/ml.

[0021] Furthermore it is particularly preferred that the concentration of the polyvinylpyrrolidone ranging from K15 to K120 is from 8 to 15 mg/ml.

[0022] Moreover it is preferred the solutions according to the invention are sterile formulations.

[0023] According to an advantageous embodiment of the invention the solutions according to the invention contain 1 or more C_{1-4} alkylester(s) of p-hydroxybenzoic acid [f)] for additional protection.

[0024] Preferably the C_{1-4} alkylester(s) of p-hydroxybenzoic acid (f)] is/are methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate.

[0025] It is also preferred that the solutions according to the invention have pH values preferably of from 4.6 to 6.0, more preferably from 5.0 to 5.9.

[0026] A special particularly preferred solution according to the invention contains:

$1x10^3$ I.U./ml of calcitonin salmon as acetate salt [a)]

3.33 mg/ml of N-(methyl)-glucamine [b)]

2.10 mg/ml of tromethamine (c)]

6.82 mg/ml of citric acid [d)]

10.00 mg/ml of polyvinylpyrrolidone [e)]

1.00 mg/ml of methyl p-hydroxybenzoate [f)]

0.10 mg/ml of propyl p-hydroxybenzoate [f)]

976.65 mg/ml of water for injectable preparations.

[0027] A further special particularly preferred solution according to the invention contains:

$2x10^3$ I.U./ml of calcitonin salmon as acetate salt [a)]

3.33 mg/ml of N-(methyl)-glucamine [b)]

2.10 mg/ml of tromethamine [c)]

6.82 mg/ml of citric acid [d)]

10.00 mg/ml of polyvinylpyrrolidone [e)]

1.00 mg/ml of methyl p-hydroxybenzoate [f)]

0.10 mg/ml of propyl p-hydroxybenzoate [f)]

976.65 mg/ml of water for injectable preparations.

[0028] The solutions according to the invention produce minimal degradation products, during the storage period. During an ageing period of 18 months they produce, a very reduced quantity of the inactive degradation product hydroxy-calcitonin. Advantageously the inventive solutions present, after 18 months of shelf-life, a total quantity of degradation product substantially less than 5 % by weight limit indicated by various pharmacopoeias [Eur. Ph. II Ed., DAB 10 (1991), BP 88, FU IX Ed.] for calcitonin salmon substance. They are very suitable for endonasal administration, when dispensed in convenient well-known delivery system.

[0029] Another more particularly preferred embodiment according to the invention contains:

400 I.U./ml of elcatonin [a)]

3.33 mg/ml of N-(methyl)-glucamine [b)]

2.10 mg/ml of tromethamine 1c)]

6.82 mg/ml of citric acid 1d)]

10.00 mg/ml of polyvinylpyrrolidone [e)]

1.00 mg/ml of methyl p-hydroxybenzoate [f)]

0.10 mg/ml of propyl p-hydroxybenzoate [f)]

976.65mg/ml of water for injectable preparations

[0030] The surprising advantages of the pharmaceutical solutions according to the invention are summarized as follows:

A) The presence of citric acid [d)], which is useful to adjust the pH values to preferably from 4.6 to 6.0, allows the exact quantity of acetic acid, contained as volatile impurity in calcitonin salmon or in carbacalcitonin (elcatonin) to be determined specifically and precisely, by using conventional analytical methods described in several publications.

In fact, if acetic acid was added to the solution instead of citric acid, it would not be possible to determine, in the formulated preparation, the quantity of the volatile impurity acetic acid (maximum 15% by weight) contained in calcitonin salmon or in carbacalcitonin (elcatonin).

B) The solution according to the invention with citric acid [d)] is organoleptically more acceptable to patients who don't tolerate the unpleasant odour of acetic acid contained in some prior art compositions on the market.

C) Citric acid [d)] has been partially buffered, in the solutions according to the invention, preferably to pH 4.6 to 6.0, by using suitable concentrations of tromethamine [c)] and N-(methyl)glucamine [b)] instead of sodium acetate, which can also develop a remarkable odour of acetic acid.

D) Polyvinylpyrrolidone ranging from K15 to K120, [e)] is purposely included into the composition for endonasal administration, since surprisingly it is suitable to prolong the time of contact between the solution and the nasal mucosa for its binding properties.

E) In the solutions of the invention, the presence of preserving agents is optional, because the manufacturing process is carried out to obtain sterile formulations. Moreover the nasal bottles are equipped with suitable pumps, characterized by absence of air introduction after actuation (dispensing the solution), eliminating, in this way the possible bacteria contamination, during usage. Therefore C_{1-4} alkylesters of p-hydroxybenzoic acid, particularly methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate, [f)] are introduced into the solutions of the invention only for additional protection, in case of an exceptional presence of bacteria.

F) More specifically for calcitonin salmon various pharmacopoeias fix an individual limit of 5 % by weight for each related substance {DAB (1991) "Verwandte Substanzen"; Eur. Ph. II Ed. "Substances apparentees"; BP 88 "Related substances"} for calcitonin salmon powder, as acetate salt, while other publications, more specifically Pharmaceutical Research Vol. 9, N. 11, 1992 ("Degradation of Synthetic Salmon Calcitonin Aqueous Solution" - Kang Choon Lee, Yoon Joong Lee, Hyun Myo Song, Chang Ju Chun and Patrick P. DeLuca) indicate that the degradation product is only the reduced calcitonin salmon (dihydro-calcitonin), when the solution presents an acidic pH. Now surprisingly it has been found that the solutions of the invention produce only minimal degradation product during the ageing period of storage.

[0031] The described embodiments of the invention may apply also to other natural or modified calcitonin, alike human calcitonin, eel calcitonin, carbacalcitonin (elcatonin), chicken calcitonin, porcine calcitonin.

[0032] The solutions according to the invention can be administered as drops, inhaler or spray, dispensed in suitable well known delivery systems.

[0033] The invention is further illustrated by the following examples.

Example 1

Preparation of 25,000 bottles (2.0 ml) of calcitonin salmon nasal spray 200 I.U./actuation

[0034] Each actuation dispensing 100 µl of solution (200 I.U. of active principle). 1 ml of the solution containing the following constituents:

Ingredient	Amount
Calcitonin salmon as acetate salt	$2x10^8$ I.U.
N-(Methyl)-glucamine	3.33 mg
Tromethamine	2.10 mg
Citric acid (pH 4.6 to 6.0)	6.82 mg
Polyvinylpyrrolidone	10.00 mg
Methyl p-hydroxybenzoate	1.00 mg
Propyl p-hydroxybenzoate	0.10 mg
Water for injectable preparations	976.65 mg

[0035] The manufacturing process is carried out with the following conventional steps:

α) 45.0 kg of water for injectable preparations are introduced in a stainless steel dissolutor.

β) In about 3 litres of water a solution is separately prepared containing:

105.0 g of trometamine +
166.5 g of N-(methyl)-glucamine +
228.5 g of citric acid

γ) After the complete dissolution of the above solution it is added to the water in the dissolutor.

δ) Under constant and slow stirring, 500.0 g of polyvinylpyrrolidone, 50.0 g of methyl p-hydroxybenzoate and 5.0 g of propyl p-hydroxybenzoate and, finally, the remaining quantity of citric acid (112.5 g) are added to yield the pH value of 4.6 to 6.0, which is adjusted, if necessary, by adding 0.1 N NaOH.

ε) Separately a mother solution of calcitonin salmon as acetate salt is prepared by dissolving 1 x 10^8 I.U. of this active principle in about 50 ml of solution resulting from step γ).

ζ) Under constant and slow stirring, the mother solution of calcitonin salmon and the remaining quantity of water are added to the dissolutor to yield 50 kg.

[0036] All manufacturing steps from α) to ζ) are carried out under nitrogen atmosphere at positive pressure.

[0037] The obtained solution is sterilized and bottled under nitrogen atmosphere at positive pressure according to the well-known methods in the Art.

Example 2

Preparation of 10,000 bottles (1.6 ml) of carbacalcitonin (elcatonin) nasal spray 40 I.U./actuation.

[0038] Each actuation dispensing 100 µl of solution (40 I.U. of active principle).
1 ml of the solution containing the following constituents:

Ingredient	Amount
Elcatonin	400 I.U.
N-(Methyl)-glucamine	3.33 mg
Tromethamine	2.10 mg
Citric acid (pH 4.6 to 6.0)	6.82 mg
Polyvinylpyrrolidone	10.00 mg
Methyl p-hydroxybenzoate	1.00 mg
Propyl p-hydroxybenzoate	0.10 mg
Water for injectable preparations	976.65 mg

[0039] The manufacturing process is carried out with the following conventional steps :

α) 13.5 Kg of water for injectable preparations are introduced in a stainless steel dissolutor.

β) In about 1 litre of water is separately prepared a solution containing :

33.6 g of tromethamine +
53.3 g of N-(Methyl)-glucamine +
104.8 g of citric acid

γ) Once the above solution has been completely dissolved, it is added to the water in the dissolutor.

δ) Under constant and slow stirring, 160.0 g of polyvinylpyrrolidone, 16.0 g of methyl p-hydroxybenzoate and 1.6 g of propyl p-hydroxybenzoate and, finally, the remaining quantity of citric acid (4.32 g) are added to yield the pH value of 4.6 to 6.0, which is adjusted, if necessary, by adding 0.1 N NaOH.

ε) Separately 6.4 10^6 I.U. of elcatonin are dissolved in about 20.0 ml of solution, resulting from step γ) thus obtaining the mother solution.

ζ) Under constant and slow stirring, the mother solution of elcatonin and the remaining quantity of water are added to the dissolutor to yield 16 Kg.

[0040] All manufacturing steps from α) to ζ) are carried out under nitrogen atmosphere at positive pressure.
[0041] The obtained solution is filtered for sterilization and subsequently bottled under nitrogen atmosphere at positive pressure according to the well-known methods in the Art.

Example 3

Stability study of calcitonin salmon nasal spray preparation of Example 1

[0042] The stability study is carried out comparing the pharmaceutical solution according to the invention of Example 1 to two formulations available on the market, in order to assess the quality and the quantity of degradation products, during an interval of 18 months at the controlled storage temperature of +2°/+8°C.
[0043] Formulation I is that indicated in Example 1, while the compared formulations II and III have the following compositions:

Formulation II: 1 ml of solution containing 550 I.U. of calcitonin salmon as acetate salt, 0.002 g of glacial acetic acid, 0.002 g of sodium acetate trihydrate, 0.0075 g of sodium chloride and water for injectable preparations q.s. to 1 ml.

Formulation III: 1 ml of solution containing 550 I.U. of calcitonin salmon as acetate salt, 0.1 mg of benzalkonium chloride, 8.5 mg of sodium chloride, 4 mg of 0.1 N hydrochloric acid and 990.025 mg of bidistilled water.

[0044] The obtained results are summarized in the following Table 1.

Table 1

	TIME 0 (Initial)		AFTER 18 MONTHS	
Formulation	Degradation products			
	hydroxy-calcitonin % by weight	dihydro-calcitonin % by weight	hydroxy-calcitonin % by weight	dihydro-calcitonin % by weight
Formulation I (Example 1)	0.13	0	2.14	0
Formulation II	0.10	0	4.31	2.58
Formulation III	0.12	0	5.06	2.37

[0045] As it may be taken from the above results, the pharmaceutical formulation of the invention (I) generates, during the considered ageing period of 18 months, remarkably minor quantities of the degradation product hydroxy-calcitonin, compared to reference formulations II and III which additionally produce another related substance indicated as dihydro-calcitonin (reduced calcitonin).

Claims

1. Pharmaceutical non inorganic saline solutions for endonasal administration comprising

a) a natural or modified calcitonin, preferably salmon or alternatively carbacalcitonin (elcatonin), or its pharmaceutically acceptable salts, characterized in that they further contain the organic excipients
b) N-(methyl)-glucamine
c) tromethamine,
d) citric acid and
e) polyvinylpyrrolidone ranging from K15 to K120.

2. Pharmaceutical solutions according to claim 1, characterized in that the calcitonin is salmon calcitonin, human calcitonin, eel calcitonin, carbacalcitonin (elcatonin), chicken calcitonin or porcine calcitonin.

3. Pharmaceutical solutions according to claim 1 or 2, characterized in that the polyvinylpyrrolidone is of the type K40.

4. Pharmaceutical solutions according to any one of claims 1 to 3, **characterized in that** they comprise:

a) the natural or modified calcitonin or its pharmaceutically acceptable salts in concentrations of 250 I.U./ml to 5,000 I.U./ml,

b) the N-(methyl)-glucamine in concentrations of 2.0 to 5.0 mg/ml,

c) the tromethamine in concentrations of 1.0 to 4.0 mg/ml,

d) the citric acid in concentrations of 5.0 to 9.0 mg/ml and

e) the polyvinylpyrrolidone ranging from K15 to K120 in concentrations of 5 to 25 mg/ml.

5. Pharmaceutical solutions according to any one of claims 1 to 4, **characterized in that** the concentration of the natural or modified calcitonin or its pharmaceutically acceptable salts is from 400 I.U. to 1,200 I.U./ml.

6. Pharmaceutical solutions according to any one of claims 1 to 5, **characterized in that** the concentration of the N-(methyl)-glucamine is from 2.5 to 4.0 mg/ml.

7. Pharmaceutical solutions according to any one of claims 1 to 6, **characterized in that** the concentration of tromethamine is from 1.5 to 2.5 mg/ml.

8. Pharmaceutical solutions according to any one of claims 1 to 7, **characterized in that** the concentration of the citric acid is from 6.0 to 8.0 mg/ml.

9. Pharmaceutical solutions according to any one of claims 1 to 8, **characterized in that** the concentration of the polyvinylpyrrolidone ranging from K15 to K120 is from 8 to 15 mg/ml.

10. Pharmaceutical solutions according to any one of claims 1 to 9, **characterized in that** they are sterile formulations.

11. Pharmaceutical solutions according to any one of claims 1 to 10, **characterized in that** they also contain 1 or more C_{1-4} alkylesters of p-hydroxybenzoic acid for additional protection.

12. Pharmaceutical solutions according to any one of claims 1 to 11, **characterized in that** the C_{1-4} alkylesters of p-hydroxybenzoic acid is methyl p-hydroxybenzoate and/or propyl p-hydroxybenzoate.

13. Pharmaceutical solutions according to any one of claims 1 to 12, **characterized in that** they have pH values of from 4.6 to 6.0.

14. Pharmaceutical solutions according to any one of claims 1 to 13, **characterized in that** they have pH values of from 5.0 to 5.9.

15. Pharmaceutical solutions according to any one of claims 1 to 14, **characterized in that** they comprise:

$1x10^3$ I.U./ml of calcitonin salmon as acetate salt
3.33 mg/ml of N-(methyl)-glucamine
2.10 mg/ml of tromethamine
6.82 mg/ml of citric acid
10.00 mg/ml of polyvinylpyrrolidone
1.00 mg/ml of methyl p-hydroxybenzoate
0.10 mg/ml of propyl p-hydroxybenzoate
976.65 mg/ml of water for injectable preparations

16. Pharmaceutical solutions according to any one of claims 1 to 15, **characterized in that** they comprise:

2×10^3 I.U./ml of calcitonin salmon as acetate salt
3.33 mg/ml of N-(methyl)-glucamine
2.10 mg/ml of tromethamine
6.82 mg/ml of citric acid
10.00 mg/ml of polyvinylpyrrolidone
1.00 mg/ml of methyl p-hydroxybenzoate
0.10 mg/ml of propyl p-hydroxybenzoate
976.65 mg/ml of water for injectable preparations

17. Pharmaceutical solutions according to any one of claims 1 to 16, **characterized in that** they comprise:

400 I.U./ml of elcatonin
3.33 mg/ml of N-(methyl)-glucamine
2.10 mg/ml of tromethamine
6.82 mg/ml of citric acid
10.00 mg/ml of polyvinylpyrrolidone
1.00 mg/ml of methyl p-hydroxybenzoate
0.10 mg/ml of propyl p-hydroxybenzoate
976.65 mg/ml of water for injectable preparations

18. Pharmaceutical solutions, according to any one of claims 1 to 17, producing during 18 months storage interval, substantially less than 5 wt % degradation products.

19. A pharmaceutical solution as claimed in claim 17, wherein the main degradation products are hydroxycalcitonins.

Patentansprüche

1. Pharmazeutische nicht-anorganische Salzlösungen zur endonasalen Verabreichung, umfassend

a) ein natürliches oder modifiziertes Calcitonin, vorzugsweise aus Lachs, oder alternativ, Carbacalcintonin (Elcatonin), oder die pharmazeutisch annehmbaren Salze davon, **dadurch gekennzeichnet, dass** sie ferner die Arzneimittelträger
b) N-(Methyl)-glucamin,
c) Tromethamin,
d) Zitronensäure und
e) Polyvinylpyrrolidon, reichend von K15 bis K120, enthalten.

2. Pharmazeutische Lösungen nach Anspruch 1, **dadurch gekennzeichnet, dass** das Calcitonin Lachscalcitonin, menschliches Calcitonin, Aalcalcitonin, Carbacalcitonin (Elcatonin), Huhncalcitonin oder Schweinecalcitonin ist.

3. Pharmazeutische Lösungen nach Anspruch 1 oder 2, **dadurch gekennzeichnet, dass** das Polyvinylpyrrolidon vom Typ K40 ist.

4. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, dass** sie umfassen:

a) natürliches oder modifiziertes Calcitonin oder die pharmazeutisch annehmbaren Salze davon in Konzentrationen von 250 I.U./ml bis 5000 I.U./ml,
b) N-(Methyl)-glucamin in Konzentrationen von 2,0 bis 5,0 mg/ml,
c) Tromethamin in Konzentrationen von 1,0 bis 4,0 mg/ml,
d) Zitronensäure in Konzentrationen von 5,0 bis 9,0 mg/ml und
e) Polyvinylpyrrolidon, reichend von K15 bis K120, in Konzentrationen von 5 bis 25 mg/ml.

5. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, dass** die Konzentration

des natürlichen oder modifizierten Calcitonins oder der pharmazeutisch annehmbaren Salze davon 400 I.U. bis 1200 I.U./ml ist.

6. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 5, **dadurch gekennzeichnet, dass** die Konzentration des N-(Methyl)-glucamins 2,5 bis 4,0 mg/ml ist.

7. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, dass** die Konzentration des Tromethamins 1,5 bis 2,5 mg/ml ist.

8. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** die Konzentration der Zitronensäure 6,0 bis 8,0 mg/ml ist.

9. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 8, **dadurch gekennzeichnet, dass** die Konzentration des Polyvinylpyrrolidons, reichend von K15 bis K120, 8 bis 15 mg/ml ist.

10. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 9, **dadurch gekennzeichnet, dass** sie sterile Formulierungen sind.

11. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 10, **dadurch gekennzeichnet, dass** sie auch einen oder mehrere C_{1-4}-Alkylester von p-Hydroxybenzoesäure zum zusätzlichen Schutz umfassen.

12. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 11, **dadurch gekennzeichnet, dass** die C_{1-4}-Alkylester der p-Hydroxybenzoesäure Methyl-p-hydroxybenzoat und/oder Propyl-p-hydroxybenzoat sind.

13. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 12, **dadurch gekennzeichnet, dass** sie pH-Werte von 4,6 bis 6,0 haben.

14. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 13, **dadurch gekennzeichnet, dass** sie pH-Werte von 5,0 bis 5,9 haben.

15. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 14, **dadurch gekennzeichnet, dass** sie umfassen:

1×10^3 I.U./ml Lachscalcitonin als Acetatsalz
3,33 mg/ml N-(Methyl)-glucamin
2,10 mg/ml Tromethamin
6,82 mg/ml Zitronensäure
10,00 mg/ml Polyvinylpyrrolidon
1,00 mg/ml Methyl-p-hydroxybenzoat
0,10 mg/ml Propyl-p-hydroxybenzoat
976,65 mg/ml Wasser für injizierbare Zubereitungen.

16. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 15, **dadurch gekennzeichnet, dass** sie umfassen:

2×10^3 I.U./ml Lachscalcitonin als Acetatsalz
3,33 mg/ml N-(Methyl)-glucamin
2,10 mg/ml Tromethamin
6,82 mg/ml Zitronensäure
1 0,00 mg/ml Polyvinylpyrrolidon
1,00 mg/ml Methyl-p-hydroxybenzoat
0,10 mg/ml Propyl-p-hydroxybenzoat
976,65 mg/ml Wasser für injizierbare Zubereitungen.

17. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 16, **dadurch gekennzeichnet, dass** sie umfassen:

400 I.U./ml Elcatonin
3,33 mg/ml N-(Methyl)-glucamin
2,10 mg/ml Tromethamin
6,82 mg/ml Zitronensäure

10,00 mg/ml Polyvinylpyrrolidon
1,00 mg/ml Methyl-p-hydroxybenzoat
0,10 mg/ml Propyl-p-hydroxybenzoat
976,65 mg/ml Wasser für injizierbare Zubereitungen.

18. Pharmazeutische Lösungen nach einem der Ansprüche 1 bis 17, die während eines Aufbewahrungszeitraums von 18 Monaten wesentlich weniger als 5 Gew.-% Zersetzungsprodukte bilden.

19. Pharmazeutische Lösung nach Anspruch 17, worin die Hauptzersetzungsprodukte Hydroxycalcitonine sind.

Revendications

1. Solutions salines pharmaceutiques non inorganiques pour administration endonasale, comprenant

   a) une calcitonine naturelle ou modifiée, de préférence la calcitonine de saumon ou, en variante, la carbacalcitonine (elcatonine), ou un de ses sels pharmaceutiquement acceptables, **caractérisées en ce qu'elles** contiennent en outre les excipients organiques suivants :
   b) de la N-(méthyl)-glucamine
   c) de la trométhamine,
   d) de l'acide citrique, et
   e) de la polyvinylpyrrolidone allant de K15 à K120.

2. Solutions pharmaceutiques suivant la revendication 1, **caractérisées en ce que** la calcitonine est la calcitonine de saumon, la calcitonine humaine, la calcitonine d'anguille, la carbacalcitonine (elcatonine), la calcitonine de poulet ou la calcitonine porcine.

3. Solutions pharmaceutiques suivant la revendication 1 ou 2, **caractérisées en ce que** la polyvinylpyrrolidone est du type K40.

4. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 3, **caractérisées en ce qu'elles** comprennent :

   a) la calcitonine naturelle ou modifiée ou de ses sels pharmaceutiquement acceptables, à des concentrations de 250 U.I./ml à 5000 U.I./ml,
   b) la N-(méthyl)-glucamine à des concentrations de 2,0 à 5,0 mg/ml,
   c) la trométhamine à des concentrations de 1,0 à 4,0 mg/ml,
   d) l'acide citrique à des concentrations de 5,0 à 9,0 mg/ml, et
   e) la polyvinylpyrrolidone allant de K15 à K120 à des concentrations de 5 à 25 mg/ml.

5. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 4, **caractérisées en ce que** la concentration de la calcitonine naturelle ou modifiée ou de ses sels pharmaceutiquement acceptables est comprise dans l'intervalle de 400 U.I. à 1200 U.I./ml.

6. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 5, **caractérisées en ce que** la concentration de N-(méthyl)-glucamine est comprise dans l'intervalle de 2,5 à 4,0 mg/ml.

7. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 6, **caractérisées en ce que** la concentration de trométhamine est comprise dans l'intervalle de 1,5 à 2,5 mg/ml.

8. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 7, **caractérisées en ce que** la concentration d'acide citrique est comprise dans l'intervalle de 6,0 à 8,0 mg/ml.

9. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 8, **caractérisées en ce que** la concentration de polyvinylpyrrolidone allant de K15 à K120 est comprise dans l'intervalle de 8 à 15 mg/ml.

10. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 9, **caractérisées en ce qu'elles** consistent en des formulations stériles.

11. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 10, **caractérisées en ce qu'elles** contiennent également un ou plusieurs esters d'alkyle en C_1 à C_4 d'acide p-hydroxybenzoïque pour conférer une protection supplémentaire.

12. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 11, **caractérisées en ce que** les esters d'alkyle en C_1 à C_4 d'acide p-hydroxybenzoïque consistent en p-hydroxybenzoate de méthyle et/ou p-hydroxybenzoate de propyle.

13. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 12, **caractérisées en ce qu'elles** ont des valeurs de pH de 4,6 à 6,0.

14. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 13, **caractérisées en ce qu'elles** ont des valeurs de pH de 5,0 à 5,9.

15. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 14, **caractérisées en ce qu'elles** comprennent :

$1x10^3$ U.I./ml de calcitonine de saumon sous forme d'un sel consistant en acétate
3,33 mg/ml de N-(méthyl)-glucamine
2,10 mg/ml de trométhamine
6,82 mg/ml d'acide citrique
10,00 mg/ml de polyvinylpyrrolidone
1,00 mg/ml de p-hydroxybenzoate de méthyle
0,10 mg/ml de p-hydroxybenzoate de propyle
976,65 mg/ml d'eau pour préparations injectables.

16. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 15, **caractérisées en ce qu'elles** comprennent :

$2x10^3$ U.I./ml de calcitonine de saumon sous forme d'un sel consistant en acétate
3,33 mg/ml de N-(méthyl)-glucamine
2,10 mg/ml de trométhamine
6,82 mg/ml d'acide citrique
10,00 mg/ml de polyvinylpyrrolidone
1,00 mg/ml de p-hydroxybenzoate de méthyle
0,10 mg/ml de p-hydroxybenzoate de propyle
976,65 mg/ml d'eau pour préparations injectables.

17. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 16, caractérisées en ce qu'elles comprennent :

400 U.I./ml d'elcatonine
3,33 mg/ml de N-(méthyl)-glucamine
2,10 mg/ml de trométhamine
6,82 mg/ml d'acide citrique
10,00 mg/ml de polyvinylpyrrolidone
1,00 mg/ml de p-hydroxybenzoate de méthyle
0,10 mg/ml de p-hydroxybenzoate de propyle
976,65 mg/ml d'eau pour préparations injectables.

18. Solutions pharmaceutiques suivant l'une quelconque des revendications 1 à 17, formant pendant un intervalle de stockage de 18 mois une quantité substantiellement inférieure à 5 % en poids de produits de dégradation.

19. Solution pharmaceutique suivant la revendication 17, dans laquelle les produits de dégradation principaux sont des hydroxycalcitonines.